Vasopressin Antagonists Effective for Hyponatremia

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Satavaptan and conivaptan seem effective in treating dilutional hyponatremia, a frequent consequence of heart failure and of renal failure.

Data supporting the efficacy of the vasopressin receptor antagonists for this indication were presented in two posters at the annual meeting of the American Society of Nephrology. Satavaptan has not yet received Food and Drug Administration approval. Conivaptan, which was approved in 2005 for euvolemic hyponatremia, received approval in early 2007 for dilutional (hypervolemic) hyponatremia.

The conivaptan study was supported by Astellas Pharma US Inc. and the satavaptan study was supported by Sanofi Aventis. Both companies manufacture the vasopressin receptor antagonists.

Safety and efficacy in patients with heart failure (HF) are noteworthy findings because the current labeling for conivaptan says the drug is not indicated for the treatment of HF and should be used in these patients only when the expected benefit of increased serum sodium outweighs the potential adverse events.

Dr. Stephen R. Goldsmith of the University of Minnesota, Minneapolis, and his colleagues reported that conivaptan was effective at dosages of 20-40 mg/day, yielding significant increases in serum sodium concentration and in the area under the serum sodium concentration curve, compared with placebo.

The study was a retrospective analysis of two trials of conivaptan, one a randomized controlled trial and the other an open-label trial of patients with euvolemic and hypervolemic (dilutional) hyponatremia. For their presentations, they limited analysis to the 28 patients in the randomized controlled trial and the 69 patients in the open-label trial with hypervolemic hyponatremia.

The patients had serum sodium concentrations of 115-130 mEq/L and fasting blood glucose levels of less than 275 mg/dL. Their mean age was 71 years, and 62% had heart failure. They received either a 20-mg IV loading dose of conivaptan or placebo by 30-minute IV infusion followed by a continuous 4-day IV infusion.

Conivaptan infusion was associated with increases in serum sodium concentration over baseline of 4 mEq/L or more at all dosages. This increase occurred in a median of 58 hours at the lowest dosage (20 mg/day) and in a median of 24 hours at the higher dosages (40 and 80 mg/day). Most of the patients treated with conivaptan achieved at least a 6-mEq/L increase in serum sodium concentration over baseline or normal serum sodium concentrations at or above 135 mEq/L.

Significantly more serious adverse events occurred in those treated with conivaptan, compared with those on placebo. Deaths occurred at a similar frequency across all four groups. The most common adverse events were infusion-site phlebitis, infusion-site reactions, vomiting, and hypotension.

Conivaptan was as effective and as safe in patients with HF as it was in patients with other conditions. Still, the drug is intended to treat the hyponatremia that accompanies HF and not HF itself, Dr. Goldsmith emphasized in an interview. But, "since there is inevitable decongestion with a vaptan as a consequence of the free water excretion, one does, of course, 'treat' the [heart failure] to some extent."

In the other presentation, Dr. Doron Aronson of Rambam Medical Center, Haifa, Israel, and colleagues found 50 mg/day of satavaptan was superior to placebo with respect to the sodium responder rate.

That study involved 118 patients randomized to receive either placebo or satavaptan at 25 mg/day or 50 mg/day. All of the patients had dilutional hyponatremia with serum sodium concentrations between 115 and 132 mEq/L. Heart failure was the cause of hyponatremia in 76% of the patients. The study excluded those with liver cirrhosis or the syndrome of inappropriate antidiuretic hormone secretion.

At the end of the 4-day double-blind period, 61% of the patients in the 50-mg group had a sodium response, compared with 27% in the placebo group, a significant difference. The sodium responder rate seemed higher in the 25-mg group than in the placebo group, but this figure did not quite reach statistical significance.

The median time to response was 3.3 days in the 25-mg group and 2.8 days in the 500-mg group, both significantly shorter than that for placebo, where the median time to response was more than 4 days.

Significantly more patients in the satavaptan groups than in the placebo group had overly rapid correction of serum sodium (increases of 12 mEq/L or more within 24 hours). Other adverse events in the satavaptan groups were atrial fibrillation, a prolonged QTc interval, hypotension, hypertension, and pyrexia. ■

Pioglitazone May Lower Cardiovascular Risk in CKD Patients

BY KERRI WACHTER
Senior Writer

Treatment with pioglitazone might help lower the risk of cardiovascular events in patients with chronic kidney disease, the results of a large study suggest.

"CKD, as defined by a glomerular filtration rate of less than 60 mL/min per 1.73 m^2, is an independent risk factor for major adverse cardiovascular events and death in this high-risk population," the researchers said. "Our data suggest patients with diabetes and high risk identified by CKD can be treated effectively with pioglitazone."

The study, by Dr. Christian A. Schneider of the University of Cologne (Germany), and his associates, was funded by Takeda Pharmaceutical Co., which makes Actos (pioglitazone). All of the authors had potential conflicts of interest involving several pharmaceutical companies.

They assessed the effect of CKD on cardiovascular outcomes using data from the Prospective Pioglitazone Clinical Trial in Macrovascular Events, which compared the effects of the thiazolidinedione pioglitazone with placebo on cardiovascular outcomes in patients with diabetes and a history of macrovascular disease. A total of 5,238 patients aged 35-75 years with type 2 diabetes and documented evidence of macrovascular disease were enrolled in the trial.

Patients were randomly assigned to receive pioglitazone (2,605) or placebo (2,633), in addition to their existing glucose-lowering and cardiovascular medications. Pioglitazone was administered at 15 mg/day for the first month, 30 mg/day for the second month, and 45 mg/day for the third month. At baseline, serum creatinine was measured. Urinary albumin concentration was measured locally at the beginning and end of the study. Blood samples were collected for creatinine measurement to observe the natural history of renal disease.

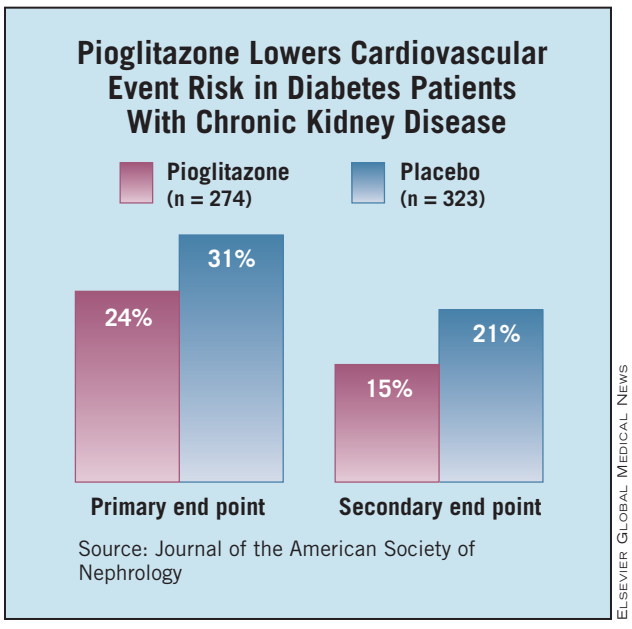
The primary end point was time from randomization to the composite end point of all-cause mortality, nonfatal myocardial infarction (including silent MI), stroke, acute coronary syndrome, coronary/carotid arterial intervention, leg revascularization, or amputation above the ankle. The secondary end point was time to the first event of all-cause mortality, MI (excluding silent MI), and stroke (J. Am. Soc. Nephrol. 2008;19[1]:182-7).

Glomerular filtration rate data were available for 5,154 patients. CKD was defined as a GFR less than 60 mL/min per 1.73 m^2. A total of 597 patients met this criterion. Patients with CKD were older, had a longer duration of diabetes, and had a higher prevalence of hypertension. However, there were no differences in baseline characteristics between patients with CKD who received pioglitazone and those with CKD who received placebo.

In patients with CKD, the incidence of the primary end point was 28%, compared with 20% in patients without the disease. The incidence of the secondary end point was 18% in patients with CKD, compared with 12% in those without. More patients with CKD died of any cause (11%) than did those without the disease (6%).

"Multivariate analysis showed the presence of CKD was an independent risk factor for the primary composite end point," the researchers wrote.

Among patients with CKD, 24% of those on pioglitazone met the primary end point, compared with 31% of the placebo group. Likewise, fewer patients on pioglitazone (15%) met the secondary end point, compared with those on placebo (21%). All-cause mortality rates were 8% for the pioglitazone group, compared with 14% for the placebo group. Overall, in the group with CKD, "there was a nonsignificant 25% risk reduction for pioglitazone relative to placebo for the primary end point and a significant 34% relative risk reduction for the secondary end point," the investigators wrote.



Elsevier Global Medical News

In comparison, in patients without CKD, 19% on pioglitazone met the primary end point, compared with 20% in the placebo group. Similar results were seen for the secondary end point—11% of those on pioglitazone versus 12% of those on placebo. All-cause mortality was 6.0% for those on pioglitazone, compared with 5.7% for placebo.

In addition, during the mean 3-year treatment period, GFR for patients with CKD declined by 5.4 and 2.7 mL/min per 1.73 m^2 in the pioglitazone and placebo groups, respectively. Among patients without CKD at baseline, 20.4% in the pioglitazone group and 16.3% in the placebo group developed CKD during the study.

The authors offered possible mechanisms for the increased risk of cardiovascular events with CKD. First, CKD often coexists with other cardiovascular risk factors. Second, "impaired kidney function is associated with elevated markers of inflammation" and other cardiovascular risk factors. Third, patients with renal disease are less likely to receive efficacious therapies to prevent cardiovascular disease.

But Dr. David M. Nathan, director of the Diabetes Center at Massachusetts General Hospital, in Boston, and professor of medicine at Harvard Medical School, criticized the analysis, noting that the PROactive study on which it was based was controversial. One of the criticisms of that study is that undue emphasis was given to a secondary end point, which contrasted with the results of the prespecified primary end point (BMJ 2005;331:836-8). He said GFR declined by a greater degree in patients on pioglitazone than in those on placebo and that more patients in the pioglitazone group who did not have CKD at baseline went on to develop CKD, compared with their placebo counterparts.

The authors noted study limitations: Data were collected prospectively, but the analysis was done retrospectively; and treatment randomization was not stratified by CKD. ■